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| <b>AstraZeneca</b>                 | <b>MEDI2338</b>   |
| <b>Mechanism of Action</b>         | Interleukin-18 (IL-18) inhibitor<br><a href="http://www.ncbi.nlm.nih.gov/gene/3606">http://www.ncbi.nlm.nih.gov/gene/3606</a>   |
| <b>Overview</b>                    | MEDI2338 is a high affinity human IgG1 monoclonal antibody that binds human IL-18. IL-18 is a pro-inflammatory cytokine involved in both innate and acquired immune responses and has been implicated in the pathology of respiratory and cardiovascular diseases such as chronic obstructive pulmonary disease and coronary artery disease, respectively. MEDI2338 is a high affinity ( $K_d$ = 60-70pM) human, null effector, IgG1 kappa monoclonal antibody that binds to human IL-18 and blocks the interaction with the IL-18R. MEDI2338 modulates disease relevant mediators in a range of <i>in vitro</i> primary leukocyte cell assays. MEDI2338 inhibited IL-18 mediated interferon- $\gamma$ release from human and cynomolgus monkey peripheral blood mononuclear cells (stimulated with LPS plus rhIL-12 to produce endogenous IL-18), with $IC_{50}$ = 0.15 nM and 0.28 nM, respectively. MEDI2338 inhibited IL-18 induced up-regulation of CD11b on primary human neutrophils with $IC_{50}$ = 2 nM and inhibited IL-18 dependent induction of reactive oxygen species produced by human neutrophils with $IC_{50}$ = 0.2nM. MEDI2338 does not bind rodent IL-18, prohibiting its direct evaluation in rodent <i>in vivo</i> pharmacology models. A commercially sourced rat anti-mouse IL-18 antibody was used to study the effects of IL-18 blockade in preclinical respiratory and cardiovascular models of disease and although not a perfect surrogate for MEDI2338 positive data were observed in these models. |
| <b>Safety/Tolerability</b>         | Rodents were not considered relevant preclinical species based on the low human sequence identity of IL-18 (62.8%) and lack of binding of MEDI2338 to rodent IL-18. Cynomolgus monkey ( <i>Macaca fascicularis</i> ) was selected as the species for pre-clinical safety studies because: 1) the sequence similarity to human (96% identity); 2) MEDI2338 binds to an IL-18 epitope where the amino acids are conserved; and 3) MEDI2338 binds with similar affinity to, and functionally inhibits, IL-18 from both species <i>in vitro</i> . In monkeys MEDI2338 exhibited dose-proportional increases in exposure, with mean $t_{1/2}$ = 11.6-13.5 days and a subcutaneous (sc) bioavailability estimated at about 75%. Despite full suppression of IL-18 levels no MEDI2338-related adverse effects were observed in the 13 week repeat dose GLP toxicology study. The NOAEL was 100 mg/kg iv, the highest dose level tested. A 4-week repeat dose non-GLP dose range finding toxicity study in monkeys suggested a 50 mg/kg sc NOAEL, the highest dose level tested.<br><br>MEDI2338 has been studied in a Phase 1 single ascending dose (SAD) study in stable, mild to moderate, chronic obstructive pulmonary disease (COPD) patients. Five cohorts received 10-1000 mg MEDI2338 (clinicaltrials.gov, NCT01322594). Data from the Phase 1 single ascending dose (SAD) study is being analyzed currently and a completed study report is not expected before Sept 2012.  |
| <b>Additional Information</b>      | None  |
| <b>Suitable for and Exclusions</b> | Preclinical safety and pharmacology data support the future clinical utility in inflammatory disease therapy, however an appraisal of early clinical safety data will be required to guide future clinical evaluation of this molecule. Clinical studies with dosing regimens in excess of 3 months (limited by current level of preclinical toxicology cover) should be excluded. There are no data to support use in pediatric populations.<br><br>Proposals for use in ophthalmology or dermatology are not of interest.   |
| <b>Clinical Trials</b>             | <a href="http://clinicaltrials.gov/ct2/results?term=MEDI233">http://clinicaltrials.gov/ct2/results?term=MEDI233</a>   |
| <b>Publications</b>                | None  |